ClinicalEvidence

Postherpetic neuralgia

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ABSTRACT

INTRODUCTION: Although there is some variability (depending on the definition of postherpetic neuralgia), about 10% of those with zoster will have persisting pain 1 month after the rash.The main risk factor for postherpetic neuralgia is increasing age; it is uncommon in people aged <50 years, but develops in 20% of people aged 60 to 65 years who have had acute herpes zoster, and in >30% of those people aged >80 years. Up to 2% of people with acute herpes zoster may continue to have postherpetic pain for 5 years or more. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions aimed at preventing herpes zoster and subsequent postherpetic neuralgia? What are the effects of interventions during an acute attack of herpes zoster aimed at preventing postherpetic neuralgia? What are the effects of interventions to relieve established postherpetic neuralgia after the rash has healed? We searched: Medline, Embase, The Cochrane Library, and other important databases up to December 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 41 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: corticosteroids, capsaicin, dextromethorphan, dressings, gabapentin, herpes zoster vaccine, oral antiviral agents, oral opioid analgesics, lidocaine, topical antiviral agents (idoxuridine), and tricyclic antidepressants.

QUESTIONS

INTERVENTIONS

PREVENTING HERPES ZOSTER

Beneficial

TREATING ACUTE HERPES ZOSTER

Unknown effectiveness

Likely to be ineffective or harmful

TREATING POSTHERPETIC NEURALGIA

Beneficial

Likely to be beneficial

Unknown effectiveness

To be covered in future updates

Carbamazepine

Pregabalin

Key points

- Pain that occurs after resolution of acute herpes zoster infection can be severe. It may be accompanied by itching and follows the distribution of the original infection. All definitions of postherpetic neuralgia (PHN) are arbitrary and range from 1 month to 6 months after the rash. For clinical trials, neuralgia of 3 months or more has become the most common definition, because resolution of neuralgia after 3 months is slow.

The main risk factor for postherpetic neuralgia is increasing age; it is uncommon in people aged <50 years, but develops in 20% of people aged 60 to 65 years who have had acute herpes zoster, and in >30% of those people aged >80 years.

Up to 2% of people with acute herpes zoster may continue to have postherpetic pain for 5 years or more.

- Oral antiviral agents (aciclovir, famciclovir, valaciclovir, and netivudine), taken during acute herpes zoster infection, may reduce the duration of postherpetic neuralgia compared with placebo.

We don't know whether topical antiviral drugs, tricyclic antidepressants, or corticosteroids taken during an acute attack reduce the risks of postherpetic neuralgia, as we found few good-quality studies.

Corticosteroids may cause dissemination of herpes zoster infection.

We don't know whether the use of dressings, oral opioids, or gabapentin during an acute attack reduces the risk of postherpetic neuralgia, as we found no studies.

There is limited evidence that gabapentin and oxycodone may reduce the acute pain of herpes zoster.

Gabapentin and tricyclic antidepressants (amitriptyline, nortriptyline) and some opioids (oxycodone, morphine, methadone) may reduce pain at up to 8 weeks in people with established postherpetic neuralgia compared with placebo.

Topical lidocaine may be more effective than placebo in treating postherpetic neuralgia.

Adverse effects of tricyclic antidepressants are dose related and may be less frequent in postherpetic neuralgia compared with depression, as lower doses are generally used.

Opioid analgesic drugs are likely to be effective in reducing pain associated with postherpetic neuralgia, but they can cause sedation and other well-known adverse effects.

We don't know whether dextromethorphan is effective at reducing postherpetic neuralgia.

We don't know whether topical counterirritants such as capsaicin reduce postherpetic neuralgia.

The zoster vaccine should be used as the primary prevention for herpes zoster and postherpetic neuralgia in people aged >60 years.

We don't know whether serotonin–norepinephrine reuptake inhibitors (SNRIs; duloxetine, venlafaxine) or selective serotonin reuptake inhibitors are effective at reducing postherpetic neuralgia.

DEFINITION

Postherpetic neuralgia (PHN) is pain that often follows resolution of acute herpes zoster and healing of the zoster rash. Herpes zoster is caused by reactivation of latent varicella zoster virus (human herpes virus 3) in people who have been rendered partially immune by a previous attack of chickenpox. Herpes zoster infects the sensory ganglia and their areas of innervation. It is characterised by pain in the distribution of the affected nerve, and crops of clustered vesicles over the area. Pain may occur days before rash onset, or no rash may appear (zoster sine herpete), making the diagnosis difficult. PHN is thought to arise following nerve damage caused by herpes zoster. PHN can be severe, accompanied by itching, and it follows the distribution of the original infection. All definitions of PHN are arbitrary and range from 1 month to 6 months after the rash. For clinical trials, neuralgia of 3 months or more has become the most common definition, because resolution of neuralgia after 3 months is slow. Thus, the number of people required for parallel and crossover trial designs is limited, and there is less risk of a period effect in a crossover trial.

INCIDENCE/ PREVALENCE

In a UK general practice survey of between 3600 and 3800 people, the annual incidence of herpes zoster was 3.4/1000. [1] Incidence varied with age. Herpes zoster was relatively uncommon in people aged <50 years (<2/1000/year), but rose to between 5/1000 and 7/1000 per year in people aged 50 to 79 years, and 11/1000 in people aged 80 years and older. A population-based study in the Netherlands reported a similar incidence (3.4/1000/year) and a similar increase of incidence with age (3–10/1000/year in people aged >50 years). [2] Prevalence of PHN depends on when it is measured after acute infection. There is no agreed time point for diagnosis. About 10% of all ages will have PHN 1 month after the rash, but, as there is a direct relationship to age, about 50% will continue to suffer at age 60 years.

AETIOLOGY/ RISK FACTORS

The main risk factor for PHN is increasing age. In a UK general practice study (involving 3600–3800 people, 321 cases of acute herpes zoster) there was little risk in those aged <50 years, but PHN developed in >20% of people who had had acute herpes zoster aged 60–65 years, and in 34% of those aged >80 years. [1] No other risk factor has been found to predict consistently which people with herpes zoster will experience continued pain. In a general practice study in Iceland (421 people followed for up to 7 years after an initial episode of herpes zoster), the risk of PHN was 1.8% (95% CI 0.6% to 4.2%) for people aged <60 years, and the pain was mild in all cases. [3] The risk of severe pain after 3 months in people aged >60 years was 1.7% (95% CI 0% to 6.2%). Other risk factors for PHN (defined as moderate pain daily 3 months after herpes) are severe pain with herpes zoster, greater rash severity, increased neurological abnormalities in the affected dermatome (sensory

loss), the presence of a prodrome, a more pronounced immune response, and psychosocial factors. [4]

PROGNOSIS

About 2% of people with acute herpes zoster in the UK general practice survey had pain for >5 years. [1] Prevalence of pain falls as time elapses after the initial episode. Among 183 people aged >60 years in the placebo arm of a UK trial, the prevalence of pain was 61% at 1 month, 24% at 3 months, and 13% at 6 months after acute infection. [5] In one RCT, the prevalence of postherpetic pain in the placebo arm at 6 months was 35% in 72 people aged >60 years. [6] After PHN has persisted for >1 year, about 50% of people will have significant pain, and 50% will recover or be controlled with medication at a median of 2 years' follow-up. [7]

AIMS OF INTERVENTION

To prevent herpes zoster and subsequent PHN; to prevent or reduce PHN by intervention during acute attack of herpes zoster; to reduce the severity and duration of established PHN, with minimal adverse effects of treatment.

OUTCOMES

Preventing herpes zoster: **Rates of herpes zoster, rates of subsequent PHN**. *Treating acute herpes zoster to prevent PHN*: **Rates of PHN**, namely persistent pain at least 3 months after resolution of acute herpes zoster infection and healing of rash. We did not consider short-term outcomes such as rash healing or pain reduction during the acute episode. *Treating postherpetic neuralgia:* **Pain improvement** In established PHN it is difficult to assess the clinical relevance of reported changes in "average pain"; therefore, we present data as dichotomous outcomes where possible (pain absent or greatly reduced, or pain persistent). **Adverse effects of treatments**.

METHODS

Clinical Evidence search and appraisal December 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to December 2009, Embase 1980 to December 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 4 (1966 to date of issue). An additional search was carried out of the NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. In trials, the most common time point chosen for assessing the prevalence of PHN was 3 months, which we use in this review unless otherwise specified. We also consider only immunocompetent adults for this review. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 18). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of interventions aimed at preventing herpes zoster and subsequent postherpetic neuralgia?**

OPTION **HERPES ZOSTER VACCINES** New

Rates of herpes zoster

Compared with placebo Zoster vaccine is more effective at reducing the number of cases herpes zoster at 3 years (high-quality evidence).

Rates of postherpetic neuralgia

Compared with placebo Zoster vaccine is more effective at reducing the number of cases of postherpetic neuralgia at 3 years (high-quality evidence).

For GRADE evaluation of interventions for postherpetic neuralgia, **see table, p 18 .**

Benefits:

Herpes zoster vaccines versus placebo or no treatment:
We found two RCTs comparing zoster vaccines versus placebo or no treatment. [8] [9]

The first RCT (38,546 immunocompetent adults aged at least 60 years who had a history of varicella or had resided in the US for at least 30 years) compared zoster vaccine (0.5 mL of live attenuated Oka/Merck VZV vaccine) versus placebo. [8] It found that zoster vaccine reduced the proportion of confirmed cases of herpes zoster at a mean follow-up time of 3.12 years (315/19270 [1.6%] with zoster vaccine *v* 642/19,276 [3.3%] with placebo), and significantly reduced the incidence of herpes zoster per 1000 person-years (5.42 per 1000 person-years with zoster vaccine *v* 11.12 per 1000 person-years with placebo; P <0.001). It found that zoster vaccine significantly reduced the herpes zoster burden of illness (score range 0 to 1813; increasing score associated with increasing pain and discomfort) at a mean of 3.12 years (2.21 with zoster vaccine *v* 5.68 with placebo; P <0.001). The RCT also found that zoster vaccine reduced the proportion of cases of postherpetic neuralgia at a mean follow-up time of 3.12 years (27/19,270 [0.1%] with zoster vaccine *v* 80/19,276 [0.4%] with placebo; P <0.001), and significantly decreased the incidence of postherpetic neuralgia per 1000 person-years (0.46 per 1000 person-years with zoster vaccine *v* 1.38 per 1000 person-years with placebo; P <0.001) [8]

The second RCT reported only adverse effects; see harms. [9]

Harms:

Herpes zoster vaccines versus placebo or no treatment:
The first RCT found similar proportions of people with vaccine-related serious adverse effects (asthma exacerbation, symptoms of polymyalgia rheumatica, anaphylactoid reaction, and Goodpasture's syndrome) in both groups at a mean follow-up of 3.12 years (2/19,270 [0.01%] with zoster vaccine *v* 3/19,276 [0.02%] with placebo; significance not assessed). [8] The RCT found no significant difference in the proportion of people with at least one serious adverse effect at 42 days (255/19,270 [1.3%] with zoster vaccine *v* 254/19,276 [1.3%] with placebo; ARI +0.01%, 95% CI –0.2% to +0.3%). However, it found that zoster vaccine significantly increased the proportion of people with varicella-like rash at the injection site at 42 days (20/19,270 [0.1%] with zoster vaccine *v* 7/19,276 [0.04%] with placebo; ARI 0.07%, 95% CI 0.02% to 0.13%; P <0.05). In a detailed sub-study of 6616 people, to assess adverse effects in the first 42 days after vaccination, the RCT found that zoster vaccine significantly increased the proportion of people with: at least one serious adverse effect; at least one adverse effect; vaccine-related systemic adverse effects; and at least one adverse effect at the injection site (proportion of people with at least one serious adverse effect: 64/3345 [1.9%] with zoster vaccine *v* 41/3271 [1.3%] with placebo; ARI 0.7%, 95% CI 0.1% to 1.3%; P <0.05; proportion of people with at least one adverse effect: 1929/3345 [58%] with zoster vaccine *v* 1117/3271 [34%] with placebo; ARI 23.7%, 95% CI 21.3% to 26.0%; P <0.05; proportion of people with vaccine-related systemic adverse effects: 209/3345 [6%] with zoster vaccine *v* 160/3271 [5%] with placebo; ARI 1.4%, 95% CI 0.3% to 2.5%; P <0.05; proportion of people with at least one adverse effect at the injection site: 1604/3345 [48%] with zoster vaccine *v* 539/3271 [14%] with placebo; ARI 31.7%, 95% CI 28.3% to 32.6%; P <0.05). Adverse effects at the injection site included erythema, pain or tenderness, swelling, pruritus, and warmth (in order of frequency). [8]

The second RCT (21 immunocompetent adults with a negative clinical history of varicella, aged 27–69 years) enrolled participants in two stages. [9] People with low VZV antibody titre (<5 gp ELISA units/mL) were enrolled in stage one, and people with undetectable VZV antibodies were enrolled in stage two. The RCT compared zoster vaccine (50,000 PFU) versus placebo for 42 days post vaccination. The RCT reported that only two people with a baseline VZV antibody titre >5 gp ELISA units/mL suffered from at least one injection site reaction: burning (1 person), erythema (1 person), and pruritus (2 people). However, the RCT made no between-group comparisons. [9]

Comment:

The vaccine to prevent herpes zoster can be categorised as beneficial and safe in that, in the population aged 60 and older, it reduces herpes zoster by 50%, postherpetic neuralgia (PHN) by two-thirds, and burden of disease by two-thirds. [8] Therefore, even if herpes zoster occurs after vaccination, PHN is attenuated. The zoster vaccine is important because PHN is difficult to prevent with antiviral drugs and other drugs when zoster first occurs, and PHN is difficult to treat once established. The vaccine is not intended for the treatment of acute herpes zoster or PHN.

The vaccine is currently approved in the UK, US, and Canada for immunocompetent adults >60 years of age. The duration of protection is unknown but a long-term study is ongoing. The entire contents of a reconstituted, single-dose vial should be given subcutaneously, preferably into the upper arm. It is supplied as a powder with accompanying diluent and must be stored frozen (–15 °C).

After reconstitution it must be administered within 30 minutes to avoid loss of potency. The vaccine provides protection for at least 4 years and the need for a booster dose is currently unknown. Currently it must be paid for by the patient and recovered from private insurance if possible. It is not covered in the US and Canada by the government, hospitals, clinics, and some insurance companies.

A number of issues of practical clinical importance have been discussed: 1) The safety and efficacy of the vaccine in the <60 age group is unknown, although there is no reason to believe that it would be less safe or efficacious. [10] 2) A recent clear history of herpes zoster would confer immunity, and the vaccine is unlikely to be beneficial in these people, but a remote or unclear episode of shingles decades previously would make vaccination reasonable, although there are no data to support this. 3) VZV sero-positivity for Americans is 95%, whether a history of chickenpox is recalled or not, and there is evidence that vaccination of sero-negative individuals is not harmful. [9] 4) The US Centers for Disease Control (CDC) notes that there is no evidence that inactivated vaccines (influenza, pneumococcal) interfere with immune responses to other inactivated or live vaccines. [11] 5) Because the zoster vaccine is a live but attenuated vaccine, there is at least a theoretical possibility of dissemination of this virus. Obvious contraindications are lymphoproliferative diseases, chemotherapy or radiotherapy, organ transplant, and HIV positivity. According to CDC guidelines, the use of 20 mg or more of prednisone per day for 2 weeks or more would require a 3-month period after discontinuation before the vaccine is given. The risk with lupus, methotrexate or TNF inhibitor use, or chronic lymphocytic leukaemia has not been established. Diabetes mellitus, coronary disease, hypertension, and extreme old age are not contraindications.

QUESTION What are the effects of interventions during an acute attack of herpes zoster aimed at preventing postherpetic neuralgia?

OPTION ORAL ANTIVIRAL AGENTS (ORAL ACICLOVIR, FAMCICLOVIR, VALACICLOVIR, NETIVUDINE) FOR PREVENTING PHN

Rates of postherpetic neuralgia

Compared with placebo Oral aciclovir is more effective at reducing the risk of postherpetic neuralgia at 1 month after the onset of herpes zoster in immunocompetent adults; however, oral aciclovir is no more effective at reducing the risk of postherpetic neuralgia at 4 and 6 months after onset of herpes zoster rash (high-quality evidence).

Compared with placebo A higher dose of oral famciclovir is more effective at reducing the risk of postherpetic neuralgia in immunocompetent adults (high-quality evidence).

Compared with valaciclovir Oral aciclovir is no more effective at reducing the proportion of immunocompetent adults with persistent pain after 6 months (high-quality evidence).

Compared with netivudine Aciclovir may be more effective at eradicating postherpetic pain after 6 months in immunocompetent adults (low-quality evidence).

Compared with topical idoxuridine Oral aciclovir may be as effective at reducing the prevalence of postherpetic pain after 1 month in immunocompetent adults (low-quality evidence).

Compared with famciclovir Valaciclovir is as effective at reducing postherpetic neuralgia after 7 days' treatment in immunocompetent adults (high-quality evidence).

Compared with aciclovir alone Combined corticosteroids plus aciclovir may be no more effective at reducing persistent pain after 6 months (low-quality evidence).

Note

We found no clinically important results from RCTs about the effects of adding amitriptyline to oral antiviral drugs.

For GRADE evaluation of interventions for postherpetic neuralgia, **see table, p 18 .**

Benefits:

Oral aciclovir versus placebo:

We found two systematic reviews (search dates 1998 [12] and 2009 [13]) comparing oral aciclovir versus placebo. The more recent review includes all the RCTs from the first review, therefore only the more recent review will be discussed here. [13]

The review (search date 2009, 5 RCTs, 900 people) found that oral aciclovir significantly reduced the risk of postherpetic neuralgia (PHN) 1 month after the onset of acute herpetic rash compared with placebo (4 RCTs; 153/347 [44%] with aciclovir *v* 184/345 [53%] with placebo; RR 0.83, 95% CI 0.71 to 0.96; P = 0.013). However, the review found no significant difference between groups for PHN at 4 or 6 months (4 months; 3 RCTs: 38/307 [12%] with aciclovir *v* 50/302 [17%] with

placebo; RR 0.75, 95% CI 0.51 to 1.11; P = 0.15; 6 months; 2 RCTs; 476 people: RR 1.05, 95% CI 0.87 to 1.27; P = 0.62; absolute data not reported) after the onset of acute herpetic rash compared with placebo. [13]

Oral famciclovir versus placebo:
We found two systematic reviews (search dates 1998 [12] and 2009 [13]) comparing oral famciclovir versus placebo, which both reported the same RCT. Therefore only the most recent review is reported here. [13]

The review (search date 2009, 1 RCT, 419 people) found no significant difference between oral famciclovir 500 mg compared with placebo for the presence of PHN (1 RCT; 61/138 [44%] with famciclovir *v* 56/146 [38%] with placebo; RR 1.15, 95% CI 0.87 to 1.52; P = 0.32). However, the review found that oral famciclovir 750 mg significantly reduced the risk of PHN compared with placebo (1 RCT, 68/135 [50%] with famciclovir *v* 56/146 [38%] with placebo; RR 1.31, 95% CI 1.01 to 1.71; P = 0.044). Length of follow-up was not reported. [13]

Oral aciclovir versus oral valaciclovir:
We found one systematic review (search date 1998, 1 RCT, 1141 people). [12] The RCT in the review compared 7 days of aciclovir versus oral valaciclovir (a precursor of aciclovir) given three times daily for 7 or 14 days. When the results from the 7- and 14-day valaciclovir regimens were combined, those treated with valaciclovir had a lower prevalence of pain at 6 months (AR: 19% with valaciclovir for 7 or 14 days *v* 26% with aciclovir for 7 days; P = 0.02; absolute numbers not reported).

Oral aciclovir versus oral netivudine:
We found one double-blind RCT (511 people) comparing aciclovir versus netivudine, which found no significant difference between groups in time to the first pain-free period. However, it found a significantly shorter time to complete resolution of PHN with aciclovir compared with netivudine (P = 0.007). [14] It found that the proportion of people with persistent pain at 6 months was lower in people treated with aciclovir compared with netivudine (10% with aciclovir *v* 15% with netivudine; P value not reported). [14]

Oral valaciclovir versus oral famciclovir:
We found one systematic review (search date 2003, 1 RCT, [15] 597 immunocompetent people aged 50 years and over). [16] The RCT compared valaciclovir (1 g 3 times daily) versus famciclovir (500 mg 3 times daily) started within 72 hours of appearance of the rash and given for 7 days. [15] It found no significant difference between groups in resolution of PHN (HR 1.01, 95% CI 0.82 to 1.24).

Oral aciclovir versus topical idoxuridine:
See benefits of topical antiviral agents (idoxuridine), p 7 .

Addition of corticosteroids to oral antiviral agents:
See benefits of corticosteroids, p 8 .

Addition of amitriptyline to oral antiviral agents:
We found no systematic review or RCTs that evaluated the effects of amitriptyline in addition to oral antiviral drugs compared with oral antiviral drugs alone.

Harms:

The review (search date 2009) reported no significant difference in non-serious adverse effects (including nausea, vomiting, diarrhoea, and headache) between oral aciclovir and placebo (4 RCTs; 178/355 [50%] with oral aciclovir *v* 174/354 [49%] with placebo; RR 1.01, 95% CI 0.88 to 1.15; P = 0.91). The review also reported no differences for serious adverse effects during treatment in the five RCTs or within 2 weeks of stopping treatment between groups (no further data reported). [13]

One previous systematic review (search date 1993) found that the most common adverse effects reported with aciclovir were headache and nausea. [17] In placebo-controlled trials, these effects occurred with similar frequency with treatment and placebo (headache: 37% with aciclovir *v* 43% with placebo; nausea: 13% with aciclovir *v* 14% with placebo). No major adverse effects were reported in the RCTs included in the systematic review. [17] In the RCTs, famciclovir, valaciclovir, and netivudine had similar safety profiles to aciclovir. [14] [18] [19] In the RCT comparing valaciclovir versus famciclovir, the two drugs had similar safety profiles. [15]

Comment:

The idea of reducing viral replication at the onset of herpes zoster by the use of antiviral agents to prevent postherpetic neuralgia (PHN) seems reasonable. However, there are significant problems in this regard, both practically and in demonstrating this through an RCT. The practical problem lies in diagnosing herpes zoster early, as, for antiviral drugs to be optimally effective, they should

be given within 72 hours of rash onset or as soon as possible after the disease starts. This is a problem if the only symptom is segmental pain and the rash has not appeared. There is then the issue of getting the patient seen and treated, which is a problem if disease onset occurs on Friday and medical-centre staff overlook the importance of a same-day visit. Most RCTs of antiviral drugs focus on acute zoster pain and not on PHN 3 to 6 months after the acute illness. Because when all ages are considered the incidence of PHN is low after zoster (about 10% at 1 month) these studies either may not follow patients long enough or be inadequately powered.

Clinical guide:
Valaciclovir (a prodrug for aciclovir but better absorbed) and famciclovir seem equivalent, and both superior to aciclovir (which is superior to netivudine when given orally), for the acute pain of herpes zoster and for rash healing, if given within 72 hours after rash onset. Aciclovir has an advantage in that it can be administered intravenously. Aciclovir, valaciclovir, and famciclovir accelerate rash healing and acute pain resolution but may have little or no effect on PHN 6 months after rash onset.

From a practical point of view, pending further studies, it is reasonable to use either valaciclovir or famciclovir (as they seem equivalent in efficacy and adverse effects and superior to aciclovir) at the first sign of the onset of herpes zoster and preferably within 72 hours of rash onset. With acute segmental (dermatomal) pain of a burning and shock-like nature in the forehead (V1) or mid-thoracic area (common sites for herpes zoster) without rash, it is, in the author's view, reasonable and safe to use one of these antiviral drugs in the hope of preventing or attenuating acute and chronic neuropathic and inflammatory pain. The diagnosis may prove wrong or the rash may not appear, but there is no evidence that this is harmful. One article provides evidence-based, general recommendations for the management of herpes zoster that take into account clinical efficacy, adverse effects, impact on quality of life, and costs of treatment. [20]

OPTION TOPICAL ANTIVIRAL AGENTS (TOPICAL IDOXURIDINE) FOR PREVENTING PHN

Rates of postherpetic neuralgia
Compared with placebo Topical idoxuridine may be no more effective at reducing postherpetic pain after 6 months in immunocompetent adults (very low-quality evidence).

Compared with oral aciclovir Topical idoxuridine may be as effective at reducing the prevalence of postherpetic pain in immunocompetent adults (low-quality evidence).

For GRADE evaluation of interventions for postherpetic neuralgia, see table, p 18 .

Benefits: We found one systematic review (search date 1993, 4 RCTs, 431 people). [17]

Topical idoxuridine versus placebo:
Three included RCTs (242 people, mean age not reported) compared topical idoxuridine versus placebo. Owing to heterogeneity and the poor quality of the trials, the review did not report pooled results. It reported that two of the three studies found "beneficial effects" on pain reduction at 1 month (statistical analysis and P value not reported), but none of the three RCTs found any significant difference at 6 months. [17]

Topical idoxuridine versus oral aciclovir:
The review [17] included one RCT (189 people, mean age not reported) [21] that compared topical idoxuridine versus oral aciclovir. The RCT found a non-significant trend towards proportionately fewer cases of postherpetic neuralgia in the idoxuridine group compared with aciclovir (pain 1 month after rash healing: 5% with topical idoxuridine *v* 13% with oral aciclovir; reported as not significant; absolute numbers not reported). [21]

Harms: We found no reports of important adverse effects from idoxuridine. Application beneath dressings may be cumbersome.

Comment: None.

OPTION TRICYCLIC ANTIDEPRESSANTS (AMITRIPTYLINE) FOR PREVENTING PHN

Preventing postherpetic neuralgia
Compared with placebo Amitriptyline may be more effective at reducing the prevalence of postherpetic neuralgia after 6 months in immunocompetent adults (very low-quality evidence).

For GRADE evaluation of interventions for postherpetic neuralgia, see table, p 18 .

Benefits: We found one systematic review (search date 2002, 1 RCT, [6] 80 people aged >60 years). [22] The RCT found that amitriptyline 25 mg taken within 48 hours of rash onset (prescribed with or without antiviral agents, at the practitioner's discretion) and continued for 90 days, reduced the prevalence of postherpetic neuralgia at 6 months compared with placebo (pain free: 32/38 [84%] with amitriptyline with or without antiviral *v* 22/34 [65%] with placebo with or without antiviral; P <0.05; see comment below). [6]

Harms: The RCT did not report adverse effects. [6] In another RCT reported by a systematic review, amitriptyline was associated with adverse anticholinergic effects such as dry mouth, sedation, and urinary difficulties. [17]

Comment: Interpretation of the RCT is complicated because practitioners were allowed to decide whether an antiviral agent was prescribed as well as amitriptyline. [6] Blinding may also have been inadequate. [12] The result was of borderline significance, and six people who had started treatment but had not completed a full course of amitriptyline or placebo were excluded from the analysis. [6]

OPTION CORTICOSTEROIDS FOR PREVENTING PHN

Rates of postherpetic neuralgia

Compared with placebo Corticosteroids may be no more effective at reducing the prevalence of postherpetic neuralgia 6 months after the onset of acute herpetic rash in immunocompetent adults (moderate-quality evidence).

Compared with aciclovir alone Corticosteroids plus aciclovir may be no more effective at reducing the risk of postherpetic neuralgia 6 months after the onset of the acute herpetic rash in immunocompetent adults (moderate-quality evidence).

Adverse effects

There is concern that corticosteroids may cause dissemination of herpes zoster.

For GRADE evaluation of interventions for postherpetic neuralgia, see table, p 18 .

Benefits: We found one systematic review (search date 2007, 5 RCTs, 787 immunocompetent adults) comparing corticosteroids alone or in combination with antiviral drugs versus placebo alone or placebo plus antiviral drugs. [23]

Corticosteroids versus placebo or no treatment:
The review found no significant difference between corticosteroids and placebo for the presence of postherpetic neuralgia (PHN) at 6 months after the onset of acute herpetic rash (1 RCT, 2/15 [13%] with corticosteroids *v* 2/19 [11%] with placebo; RR 1.27, 95% CI 0.20 to 7.97). [23]

Corticosteroids plus aciclovir versus placebo plus aciclovir:
The review found no significant difference between corticosteroids plus aciclovir compared with placebo plus aciclovir for the presence of PHN at 6 months after the onset of acute herpetic rash (1 RCT, 9/41 [22%] with corticosteroids plus aciclovir *v* 9/37 [24%] with placebo plus aciclovir; RR 0.90, 95% CI 0.40 to 2.03). [23]

Harms: There is concern that corticosteroids might cause dissemination of herpes zoster, but there is no evidence that this is so in immunocompetent patients. [24]

Corticosteroids versus placebo:
The review reported no significant difference between corticosteroids compared with placebo for serious adverse effects (3 RCTs; 2/87 [2%] with corticosteroids *v* 1/92 [1%] with placebo; RR 2.00, 95% CI 0.19 to 21.38; P = 0.57) or non-serious adverse effects (3 RCTs; 13/87 [15%] with corticosteroids *v* 7/95 [7%] with placebo; RR 1.80, 95% CI 0.80 to 4.08; P = 0.16). [23]

Corticosteroids plus aciclovir versus placebo plus aciclovir:
The review reported no significant differences between corticosteroids plus aciclovir compared with placebo plus aciclovir in serious adverse effects (3 RCTs; 6/292 [2%] with corticosteroids plus aciclovir *v* 3/296 [1%] with placebo plus aciclovir; RR 1.88, 95% CI 0.52 to 6.82; P = 0.86) or non-serious adverse effects (3 RCTs; 49/292 [17%] with corticosteroids plus aciclovir *v* 39/296 [13%] with placebo plus aciclovir; RR 1.27, 95% CI 0.87 to 1.87; P = 0.21). [23]

Comment: None.

OPTION OPIOID ANALGESIC DRUGS (ORAL) FOR PREVENTING PHN New

We found no clinically important results from RCTs about the effects of oral opioid drugs during an acute attack of herpes zoster for the prevention of postherpetic neuralgia.

For GRADE evaluation of interventions for postherpetic neuralgia, **see table, p 18 .**

Benefits:

Oral opioid analgesic drugs versus placebo or no treatment:
We found no systematic review or RCTs.

Oral opioid analgesic drugs versus other treatments:
We found no systematic review or RCTs.

Harms:

Oral opioid analgesic drugs versus placebo or no treatment:
We found no RCTs.

Oral opioid analgesic drugs versus other treatments:
We found no RCTs.

Comment: None.

OPTION GABAPENTIN FOR PREVENTING PHN New

We found no clinically important results from RCTs about the effects gabapentin during an acute attack of herpes zoster for the prevention of postherpetic neuralgia

For GRADE evaluation of interventions for postherpetic neuralgia, **see table, p 18 .**

Benefits:

Gabapentin versus placebo or no treatment:
We found no systematic review or RCTs.

Gabapentin versus other treatments:
We found no systematic review or RCTs.

Harms:

Gabapentin versus placebo or no treatment:
We found no RCTs.

Gabapentin versus other treatments:
We found no RCTs.

Comment:

Clinical guide:
For the acute treatment of herpes zoster, it is important to keep the rash dry, clean, and lightly covered while it crusts. Calamine lotion may help with itching. If bacterial infection supervenes, a topical antibiotic may be needed. Valaciclovir and famciclovir may be given in the first 72 hours after onset of rash — or even where there is a high suspicion with only severe segmental burning and/or jabbing pain in a dermatome commonly involved in herpes zoster (i.e., forehead or mid-thoracic area), as a course of these drugs will do no harm even if the diagnosis proves wrong, and few other diseases enter the differential diagnosis. Low-dose amitriptyline (10–25 mg) and/or single-dose gabapentin 300 mg to 900 mg and/or an opioid such as oxycodone/paracetamol as needed and/or long-acting oxycodone (5 mg every 8–12 hours) or morphine short- plus long-acting (10–15 mg every 8–12 hours) are also reasonable. If this combined approach is used, patients (especially older people) should probably remain at home and under a degree of supervisions for the first few days, in case of adverse effects of medication that may result in a fall. The author considers this somewhat aggressive approach reasonable because of the potentially devastating consequences of ophthalmic zoster, which may include loss of an eye and facial scarring. None of these approaches has been shown to prevent PHN.

OPTION DRESSINGS FOR PREVENTING PHN

We found no clinically important results from RCTs about the effects of dressings during an acute attack of herpes zoster for the prevention of postherpetic neuralgia.

For GRADE evaluation of interventions for postherpetic neuralgia, **see table, p 18 .**

Benefits: We found no systematic review or RCTs examining the effects of dressings during an acute attack of herpes zoster for the prevention of postherpetic neuralgia.

Harms: We found no RCTs.

Comment: None.

QUESTION What are the effects of interventions to relieve established postherpetic neuralgia after the rash has healed?

OPTION GABAPENTIN FOR TREATING PHN

Pain improvement
Compared with placebo Gabapentin increases the likelihood of improvement in pain after 7 to 8 weeks in people with postherpetic neuralgia (high-quality evidence).

Compared with nortriptyline Gabapentin may be as effective at reducing pain in people with postherpetic neuralgia (moderate-quality evidence).

For GRADE evaluation of interventions for postherpetic neuralgia, **see table, p 18 .**

Benefits:

Gabapentin versus placebo/no treatment:
We found one systematic review (search date 2005, 2 RCTs, 428 people with post-herpetic neuralgia [PHN]) comparing gabapentin versus placebo. [25] It found that gabapentin reduced pain compared with placebo at 7 to 8 weeks (AR for improvement in pain: 89/207 [43%] with gabapentin *v* 38/221 [17%] with placebo; RR 2.50, 95% CI 1.80 to 3.48; NNT 3.9, 95% CI 3.0 to 5.7). Three subsequent systematic reviews (search dates 2004, [26] 2005, [27] and 2008 [28]) identified the same RCTs and reported similar findings (NNT 4, 95% CI 3 to 6). [27] [26] [28]

Gabapentin versus tricyclic antidepressants:
We found one systematic review (search date 2008) comparing gabapentin versus tricyclic antidepressants. [28] The review included one RCT (70 people with PHN), which compared gabapentin (up to 2700 mg) with nortriptyline (75 mg). [29] It found no significant difference between groups for pain relief (16/34 [47%] with gabapentin *v* 17/36 [47%] with nortriptyline; RR 1.00, 95% CI 0.61 to 1.64; P = 0.99). [28]

Harms:

The review did not report on the adverse effects of gabapentin specifically in people with postherpetic neuralgia. [25]

Gabapentin versus placebo/no treatment:
The first RCT included in the review [25] found that gabapentin increased adverse effects compared with placebo (somnolence: 27% with gabapentin *v* 5% with placebo; dizziness: 24% with gabapentin *v* 5% with placebo; ataxia: 7% with gabapentin *v* 0% with placebo; peripheral oedema: 10% with gabapentin *v* 3% with placebo; infection: 8% with gabapentin *v* 3% with placebo; P values not reported). [30] It found similar withdrawal rates caused by adverse effects between gabapentin and placebo (13% with gabapentin *v* 9% with placebo; P value not reported). The second RCT included in the review [25] also found that gabapentin increased adverse effects compared with placebo (somnolence: 17% with gabapentin 1800 mg *v* 20% with gabapentin 2400 mg *v* 6% with placebo; dizziness: 31% with gabapentin 1800 mg *v* 33% with gabapentin 2400 mg *v* 10% with placebo; peripheral oedema: 5% with gabapentin 1800 mg *v* 11% with gabapentin 2400 mg *v* 0% with placebo; P values not reported). [31] This RCT found that proportionately more people taking gabapentin than placebo withdrew because of adverse effects (13% with gabapentin 1800 mg *v* 18% with gabapentin 2400 mg *v* 6% with placebo; P value not reported).

Gabapentin versus nortriptyline:
The review gave no information on adverse effects. [28]

Comment:

All the RCTs of gabapentin in PHN and other neuropathic pain such as diabetic neuropathy indicate that gabapentin results in, at most, 30% of patients having 50% (moderate) relief over placebo in the context of the selected population of an RCT. Results will not be as good in clinical practice . [32]

Clinical guide:
Gabapentinoids may cause oedema and should not be used in the presence of oedema from any cause.

OPTION SELECTIVE SEROTONIN REUPTAKE INHIBITORS New

We found no clinically important results from RCTs about the effects of selective serotonin reuptake inhibitors for relieving the symptoms of established postherpetic neuralgia.

For GRADE evaluation of interventions for postherpetic neuralgia, **see table, p 18 .**

Benefits:

Selective serotonin reuptake inhibitors (SSRIs) versus placebo or no treatment:
We found no systematic review or RCTs.

SSRIs versus other treatment:
We found no systematic review or RCTs.

Harms:

SSRIs versus placebo or no treatment:
We found no RCTs.

SSRIs versus any other option within question:
We found no RCTs.

Comment: None.

OPTION SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS New

We found no clinically important results from RCTs about the effects of serotonin-norepinephrine reuptake inhibitors for relieving the symptoms of established postherpetic neuralgia.

For GRADE evaluation of interventions for postherpetic neuralgia, **see table, p 18 .**

Benefits:

Serotonin–norepinephrine reuptake inhibitors (SNRIs) versus placebo or no treatment:
We found no RCTs.

SNRIs versus other treatments:
We found no RCTs.

Harms:

SNRIs versus placebo or no treatment:
We found no RCTs.

SNRIs versus other treatments:
We found no RCTs.

Comment: None.

OPTION TRICYCLIC ANTIDEPRESSANTS TO TREAT PHN

Pain improvement
Compared with placebo Tricyclic antidepressants may be more effective at reducing pain in people with postherpetic neuralgia after 3 to 8 weeks (moderate-quality evidence).

Compared with morphine and methadone Tricyclic antidepressants may be less effective at reducing pain in people with postherpetic neuralgia (low-quality evidence).

Compared with gabapentin Nortriptyline may be as effective at reducing pain in people with postherpetic neuralgia (moderate-quality evidence).

For GRADE evaluation of interventions for postherpetic neuralgia, **see table, p 18 .**

Benefits:

We found two systematic reviews (search dates 2007, 5 RCTs, [33] and 2005, 4 RCTs) [26] comparing tricyclic antidepressants with placebo.

Tricyclic antidepressants (TCAs) versus placebo:
The first review found that TCAs significantly improved pain relief compared with placebo at 3 to 6 weeks (5 RCTs; 219 people with postherpetic neuralgia [PHN]; AR for at least moderate pain relief: 76/115 [66%] with TCAs *v* 30/104 [29%] with placebo; RR 2.33, 95% CI 1.70 to 3.19; P <0.0001). [33] One RCT (49 people with PHN, mean age 73 years) identified by this first review [33] compared four treatments: amitriptyline alone, amitriptyline plus fluphenazine (a selective serotonin reuptake inhibitor), fluphenazine alone, and placebo. [34] Data from this RCT were not included in the review's meta-analysis of dichotomous outcomes, as only continuous data were

reported. The RCT found that amitriptyline reduced visual analogue scale (VAS) pain scores compared with placebo at 8 weeks (VAS scale 0–100: VAS reduced from 55.9 to 26.6 with amitriptyline *v* from 53.92 to 48.53 with placebo; significance not reported).

The second systematic review pooled the data from the four RCTs identified in the first review [33] (248 patient episodes of PHN). It found that TCAs significantly improved pain relief compared with placebo (NNT 3, 95% CI 2 to 4). [26]

TCAs compared with opioids:
See benefits of opioids, p 12 .

TCAs compared with gabapentin:
See benefits of gabapentin, p 10 .

Harms: TCAs are associated with anticholinergic adverse effects.

TCAs versus placebo:
The first and second reviews did not report specifically on adverse effects in people with PHN. [33] [26]

One of the RCTs included in the first review reported syncope and heart block in one person taking desipramine. [35] Another RCT included in the review first found that amitriptyline significantly increased dry mouth compared with placebo. [34] A further RCT included in the first review found that proportionately more people taking amitriptyline than placebo experienced adverse effects (dry mouth, AR: 62% with amitriptyline *v* 40% with placebo; sedation, AR: 62% with amitriptyline *v* 40% with placebo; urinary difficulties, AR: 12% with amitriptyline *v* <5% with placebo). [36]

TCAs compared with opioids:
see harms of opioids, p 9 .

TCAs compared with gabapentin:
see harms of gabapentin, p 10 .

Comment: The meta-analysis is based on results after crossover. [33]

Clinical guide:
The adverse effects of tricyclic antidepressants are dose related. Adverse effects may be less pronounced when treating postherpetic neuralgia rather than depression because lower doses are used. Treatments were not assessed for >8 weeks.

Tricyclic antidepressants are not recommended for use in the presence of severe or recent myocardial injury or arrhythmia although, as stated, the risks are probably lower as doses for pain relief are lower than for depression. A tricyclic antidepressant would not be chosen for an older man with prostatism because of possible anticholinergic aggravation of urinary retention. A tricyclic antidepressant would be less likely to be used in overweight people, because they may cause appetite stimulation.

OPTION OPIOID ANALGESIC DRUGS (ORAL)

Pain improvement
Compared with placebo Tramadol may be more effective at reducing pain after 6 weeks in people with postherpetic neuralgia (low-quality evidence).

Compared with clomipramine Tramadol may be as effective, either alone or with levomepromazine, at reducing pain in people with postherpetic neuralgia (very low-quality evidence).

Compared with placebo Oxycodone, morphine, and methadone are more effective at reducing pain associated with postherpetic neuralgia (high-quality evidence).

Compared with tricyclic antidepressants Morphine and methadone may be more effective at reducing pain compared in people with postherpetic neuralgia (low-quality evidence).

For GRADE evaluation of interventions for postherpetic neuralgia, see table, p 18 .

Benefits:

Tramadol versus placebo:
We found one systematic review (search date 2008, 2 RCTs, 149 people, meta-analysis not performed) of tramadol for postherpetic neuralgia (PHN). [37] One of the included RCTs was open label and therefore does not fulfil the inclusion criteria for this review.

The RCT included in the review (127 people with PHN, mean age 67 years) found that tramadol 100 mg to 400 mg significantly reduced mean pain intensity compared with placebo after 6 weeks (measured on a visual analogue pain score: 19.9 with tramadol *v* 28.5 with placebo; P = 0.0499; RR 1.37, 95% CI 1.04 to 1.81). However, it found no significant difference between groups in mean pain assessed on a verbal rating scale after 6 weeks (P = 0.068).

Oxycodone, morphine, and methadone versus placebo:
We found one systematic review (search date 2004, 2 RCTs, 211 person-episodes of PHN) of the opioids oxycodone, morphine, and methadone. [26] A meta-analysis of both RCTs found that opioids significantly increased the proportion of people reporting benefits for PHN compared with placebo (number of people reporting benefit: 54/110 [49%] with opioids *v* 12/101 [12%] with placebo; RR 3.89, 95% CI 2.23 to 6.77; P <0.0001; NNT 3, 95% CI 2 to 4; P <0.0001). [26]

Opioids versus tricyclic antidepressants (TCAs):
The review reported a further RCT, which compared morphine and methadone versus TCAs in people with PHN. It found that morphine and methadone significantly improved pain relief compared with TCAs (NNT for TCA 4, 95% CI 2 to 8; NNT for morphine and methadone 3, 95% CI 2 to 5; no further data reported). [26]

Harms:

Tramadol versus placebo:
The RCT included in the review comparing tramadol versus placebo reported that the proportion of people reporting at least one adverse effect was similar between groups (30% with tramadol *v* 32% with placebo; significance assessment not performed). The total numbers of adverse effects reported were also similar (31% with tramadol *v* 28% with placebo; significance assessment not performed). [38]

Oxycodone versus placebo:
One review found that oxycodone significantly increased adverse effects such as constipation, nausea, and sedation compared with placebo (76% with oxycodone *v* 49% with placebo; P = 0.0074). [39]

Opioids versus tricyclic antidepressants:
In the RCT comparing tramadol versus clomipramine, the number of people withdrawing because of adverse effects was 41% for the tramadol group versus 39% for the clomipramine group (significance assessment not performed). [26]

Comment:

None.

Clinical guide:
Opioids should be considered only after all other approaches have failed. Careful screening is important particularly in relation to a personal or family history of addiction to alcohol or illegal or prescription drugs. A verbal discussion of guidelines is important and a signed agreement may be chosen. [40]

Tramadol is an interesting drug, combining a mu opioid effect with an antidepressant-like action. It has been used for pain in Europe for some years and more recently in North America. RCTs in other types of neuropathic pain such as diabetic neuropathy have shown similar results to PHN. Tramadol does not seem as potent as conventional opioids by number needed to treat (NNT) values, and it seems to have a low propensity to cause addiction. Both short-acting and long-acting (once daily) forms are available. In the author's view this drug is at least a useful alternative to codeine and codeine/paracetamol preparations, which are often ineffective (owing to lack of conversion to morphine of the active analgesic component), potentially dangerous in East Africans (owing to excessive conversion to morphine), frequently not tolerated, and limited by paracetamol ceiling doses of 4000 mg daily. As with all opioids, a careful titration upwards is important ("start low go slow").

Morphine, oxycodone, hydromorphone, transdermal fentanyl
There are no head-to-head trials showing the superiority of any particular opioid. Short- and long-acting forms of oral opioids are available. The long-acting form is preferable for chronic use. Transdermal fentanyl should not be used in opioid-naive patients as respiratory depression may occur. A "start low go slow" approach with gradual titration is prudent. Routine prescription of a stool softener and anti-nauseant (e.g., metoclopramide) may aid initial compliance. Tolerance to

most adverse effects occurs with time. Regular follow-up in the clinic setting (eventually every 2–3 months) is important, with copies of prescriptions and enquiry regarding pain relief, adverse effects, sleep, mood, sexual function, functional status, and quality of life. Careful record keeping of these data is crucial regarding regulatory body oversight and potential audits.

OPTION DEXTROMETHORPHAN

We found no clinically important results from RCTs about the effects of dextromethorphan for pain relief in established postherpetic neuralgia.

For GRADE evaluation of interventions for postherpetic neuralgia, **see table, p 18 .**

Benefits: We found no systematic review or RCT that fitted the inclusion criteria for this review.

Harms: We found no RCTs.

Comment: None.

OPTION LIDOCAINE (TOPICAL)

Pain improvement
Compared with placebo Topical lidocaine may be more effective at reducing pain in people with postherpetic neuralgia (moderate-quality evidence).

For GRADE evaluation of interventions for postherpetic neuralgia, **see table, p 18 .**

Benefits:

Lidocaine (topical) versus placebo:
We found two systematic reviews comparing topical lidocaine versus placebo in people with postherpetic neuralgia (PHN). [41] [26]

The first review (search date 2008, 3 RCTs, 335 people) found that topical lidocaine significantly improved pain relief compared with placebo (2 RCTs, 220 people; mean difference in pain relief scale score: 0.42, 95% CI 0.14 to 0.69; P = 0.003). [41]

The second review (search date 2004, 3 RCTs, 1 RCT is also reported in the first review, 123 people) did not pool data, so the individual results are reported here. [26]

The first RCT included in the review found that lidocaine patches significantly improved pain compared with placebo (improvement: 29/32 [91%] with lidocaine *v* 13/32 [40%] with placebo; RR 2.23, 95% CI 1.45 to 3.44; NNT 2, 95% CI 1 to 3). [26] The second RCT included in the review found that lidocaine patches improved pain relief compared with placebo (data not reported). The third RCT included in the review found no significant difference with lidocaine gel applied for either 24 hours under an occlusive dressing or for 8 hours with no dressing compared with placebo (data not reported).

Harms:

Lidocaine (topical) versus placebo:
The reviews reported that lidocaine patches were well tolerated, with only mild local skin reactions and no systemic adverse effects. [41] [26]

Comment:

Clinical guide:
The lidocaine patch is particularly attractive in very old or drug intolerant people, or when oral drugs are contraindicated. In other populations, it may be most effective as an adjunct to oral agents as it is of limited use in ophthalmic PHN, which is a common occurrence of this pain. This is due to cosmetic reasons and because the pain and allodynia may be within the hairline area.

OPTION CAPSAICIN (TOPICAL)

Pain improvement
Compared with placebo Topical capsaicin may be more effective at reducing pain in people with postherpetic neuralgia (low-quality evidence).

Adverse effects
Capsaicin may cause painful skin reactions (including burning, stinging, and erythema).

For GRADE evaluation of interventions for postherpetic neuralgia, **see table, p 18 .**

Benefits: We found three systematic reviews (search dates 1993, [42] 2004, [26] 2005 [27]) and one additional RCT assessing capsaicin in people with postherpetic neuralgia (PHN). [43]

Capsaicin (topical) versus placebo:
The reviews found that topical capsaicin significantly improved pain relief compared with placebo (2 RCTs, 175 people with PHN, mean age not reported; OR for complete or greatly reduced pain 0.29, 95% CI 0.16 to 0.54; see comment below). [42] [26] [27] A further meta-analysis of the two RCTs in the most recent review also found that topical capsaicin significantly improved pain relief compared with placebo in people with PHN (improvement: 50/90 [56%] with capsaicin *v* 22/85 [26%] with placebo; RR 1.98, 95% CI 1.33 to 2.95; P <0.008; NNT 3, 95% CI 2 to 6; P <0.0001). [27] The additional RCT (31 people, mean age not reported) found no significant difference in pain between capsaicin and placebo during 6 months (measured on visual analogue scale and by McGill's test; P >0.05; see comment below). [43]

Harms: **Capsaicin (topical) versus placebo:**
Reported local skin reactions included burning, stinging, and erythema. [42] These effects tended to subside with time and frequency of use. [44] In the subsequent RCT, six people had skin burning with capsaicin compared with none with placebo (P value not reported). [43]

Comment: The first review noted that the difficulty in blinding studies with capsaicin (because of skin burning) could have caused overestimation of benefit. [42] The first review also included one unpublished RCT (30 people) that found no significant difference in pain between capsaicin and placebo. It was excluded from the meta-analysis as its inclusion resulted in significant statistical and clinical heterogeneity between the RCTs. Clinical heterogeneity occurred because the RCT had used a weaker preparation of capsaicin, shorter treatment period, and different emollient vehicle. [42] In the subsequent RCT, eight people did not complete the study (5 with capsaicin *v* 3 with placebo). [43]

Clinical guide:
The current formulations are of limited use and have to be used carefully, to be repeated applied 3 times daily and for 3 to 4 weeks. A variety of strengths and formulations are available. Hands must be carefully washed after use, as capsaicin in the eye from inadvertent rubbing, or in the urethral or perianal areas, can be distressing although not harmful. For this reason, capsaicin is usually not practical for facial postherpetic neuralgia.

GLOSSARY

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Herpes zoster vaccines for prevention herpes zoster and subsequent postherpetic neuralgia: We found two RCTs comparing herpes zoster vaccines versus placebo or no treatment. [8] [9] The first RCT found that zoster vaccine reduced the number of confirmed cases of herpes zoster at a mean follow-up time of 3.12 years, and reduced the incidence of herpes zoster per 1000 person-years. It found that zoster vaccine reduced the herpes zoster burden of illness at a mean of 3.12 years. The RCT also found that zoster vaccine reduced the number of cases of postherpetic neuralgia at a mean follow-up time of 3.12 years, and decreased the incidence of postherpetic neuralgia per 1000 person-years. [8] The second RCT only reported harms; it found that adverse effects included burning, erythema, and pruritus, at 42 days post vaccination. [9] Categorised as Beneficial.

Opioid analgesic drugs (oral) for preventing postherpetic neuralgia: New option for which we found no systematic review or RCTs that assessed the effects of oral opioids during an acute attack of herpes zoster for the prevention of postherpetic neuralgia.Categorised as Unknown effectiveness.

Gabapentin for preventing postherpetic neuralgia: New option for which we found no systematic review or RCTs that assessed the effectiveness of gabapentin during an acute attack of herpes zoster for the prevention of postherpetic neuralgia. Categorised as Unknown effectiveness.

Selective serotonin reuptake inhibitors for treating postherpetic neuralgia: New option for which we found no systematic review or RCT that fulfilled our inclusion criteria. Categorised as Unknown effectiveness.

Serotonin-norepinephrine reuptake inhibitors for treating postherpetic neuralgia: New option for which we found no systematic review or RCT which fulfilled our inclusion criteria. Categorised as unknown effectiveness.

Corticosteroids for preventing postherpetic neuralgia: One systematic review added comparing corticosteroids alone versus placebo or corticosteroids plus aciclovir versus aciclovir alone. [23] It found no difference between either comparison in the prevalence of postherpetic neuralgia at 6 months after onset of acute herpetic rash in immunocompetent adults. [23] Categorisation remains Likely to be ineffective or harmful.

Gabapentin for treating postherpetic neuralgia: One systematic review added comparing gabapentin versus tricyclic antidepressants in people with PHN. [28] The review included only one RCT, which was already included in this review; therefore no data were added. Categorisation unchanged (Beneficial).

Opioids (oral) for treating postherpetic neuralgia: One systematic review updated. [37] No additional RCTs were added. Categorisation unchanged (Likely to be beneficial).

Tricyclic antidepressants for treating postherpetic neuralgia: One systematic review updated with one RCT comparing tricyclic antidepressants versus placebo. [33] It found that tricyclic antidepressants improved pain relief in people with PHN compared with placebo. [33] Categorisation unchanged (Beneficial).

Antiviral agents for preventing postherpetic neuralgia: One systematic review added comparing antiviral agents versus placebo or no treatment. [13] The review found that oral aciclovir reduced the risk of postherpetic neuralgia (PHN) after 1 month of herpes zoster compared with placebo; however, there were no differences between groups at 4 or 6 months after onset of herpes zoster. The review also reported that oral famciclovir 750 mg reduced the risk of PHN compared with placebo, but found no differences between groups for oral famciclovir 500 mg. [13] Categorisation changed from Likely to be beneficial to Unknown effectiveness as the weight of the evidence shows no differences in risk of PHN.

Lidocaine (topical) for treating postherpetic neuralgia: One systematic review added comparing topical lidocaine versus placebo. [41] It found that topical lidocaine improved pain relief compared with placebo in people with postherpetic neuralgia. [41] Categorisation changed from Unknown effectiveness to Likely to be beneficial.

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Disclaimer

TABLE **GRADE evaluation of interventions for postherpetic neuralgia**

Important outcomes	Preventing herpes zoster, preventing postherpetic neuralgia, pain improvement, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of interventions aimed at preventing herpes zoster and subsequent postherpetic neuralgia?									
1 (38,546) [8]	Rates of herpes zoster	Zoster vaccines versus placebo	4	0	0	0	0	High	
1 (38,546) [8]	Rates of postherpetic neuralgia	Zoster vaccines versus placebo	4	0	0	0	0	High	
What are the effects of interventions during an acute attack of herpes zoster aimed at preventing postherpetic neuralgia?									
5 (900) [12] [13]	Rates of postherpetic neuralgia	Oral aciclovir *v* placebo	4	0	0	0	0	High	
1 (419) [12] [13]	Rates of postherpetic neuralgia	Oral famciclovir *v* placebo	4	0	0	0	0	High	
1 (1141) [12]	Rates of postherpetic neuralgia	Oral aciclovir *v* oral valaciclovir	4	0	0	0	0	High	
1 (511) [14]	Rates of postherpetic neuralgia	Oral aciclovir *v* oral netivudine	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
1 (597) [16]	Rates of postherpetic neuralgia	Oral valaciclovir *v* oral famciclovir	4	0	0	0	0	High	
1 (189) [21]	Rates of postherpetic neuralgia	Oral aciclovir *v* topical idoxuridine	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (608) [45] [46]	Rates of postherpetic neuralgia	Oral aciclovir plus prednisolone *v* oral aciclovir alone	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results at different end points
3 (242) [17]	Rates of postherpetic neuralgia	Topical idoxuridine *v* placebo	4	–2	–1	0	0	Very low	Quality points deducted for methodological flaws and incomplete reporting of results. Consistency point deducted for heterogeneity and conflicting results at different end points
1 (80) [6]	Rates of postherpetic neuralgia	Amitriptyline *v* placebo	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, flawed blinding, and no intention-to-treat analysis. Directness point deducted for inconsistent addition of oral antiviral drugs
1 (34) [23]	Rates of postherpetic neuralgia	Corticosteroids *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (88) [23]	Rates of postherpetic neuralgia	Corticosteroids plus aciclovir *v* placebo plus aciclovir	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of interventions to relieve established postherpetic neuralgia after the rash has healed?									
2 (428) [25]	Pain improvement	Gabapentin *v* placebo	4	0	0	0	+1	High	Effect-size point added for RR >2
1 RCT (70) [29]	Pain improvement	Gabapentin *v* nortriptyline	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Important outcomes	Preventing herpes zoster, preventing postherpetic neuralgia, pain improvement, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consis-tency**	**Direct-ness**	**Effect size**	**GRADE**	**Comment**
4 (268) [33] [26]	Pain improvement	Tricyclic antidepressants *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for analysis after crossover
1 (47)] [47]	Pain improvement	Desipramine *v* amitriptyline *v* fluoxetine	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (127) [37]	Pain improvement	Tramadol *v* placebo	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results depending on scale
1 (21) [38]	Pain improvement	Tramadol *v* clomipramine alone or with levomepromazine	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, no blinding, and poor follow-up. Directness point deducted for inconsistent addition of levomepromazine
2 (211) [26]	Pain improvement	Opioids *v* placebo	4	0	0	0	+1	High	Effect-size point added for RR >2
1 RCT [26]	Pain improvement	Opioids *v* tricyclic antidepres-sants	4	–1	0	–1	0	Low	Quality point deducted for incomplete report-ing of results. Directness point deducted for lack of direct comparison
5 (394) [26] [41]	Pain improvement	Topical lidocaine *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete report-ing of results
3 (206) [42] [26] [43]	Pain improvement	Topical capsaicin *v* placebo	4	–1	–1	0	0	Low	Quality point deducted for problems with blinding. Consistency point deducted for conflicting results

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.